1.1 State-of-the-art diagnosis and treatment of hypertension in pregnancy

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Financial support

None

Conflict of interest

Both authors have been investigators and authors of cited projects and publications.

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ABSTRACT

Hypertension complicates up to 10% of pregnancies, globally. Pregnancy hypertension is defined as systolic blood pressure (BP) ≥140mmHg or a diastolic BP ≥90mmHg, based usually on measurements in office/clinic settings and using a wide variety of BP devices. The hypertensive disorders of pregnancy (HDPs) are classified into: (i) chronic hypertension diagnosed before pregnancy or 20 weeks' gestation; (ii) gestational hypertension diagnosed at ≥20 weeks; and (iii) preeclampsia, defined restrictively as gestational hypertension with proteinuria or broadly as gestational hypertension with proteinuria or an end-organ manifestation consistent with preeclampsia. Absolute BP values ≥140/90mmHg are associated with elevated maternal and perinatal risk, particularly with preeclampsia. This review will focus on antihypertensive therapy of the HDPs as a specific management strategy. Underpinning this therapy is the need for accurate measurement of BP, agreed-upon classification of pregnancy hypertension, agreed-upon BP thresholds for enhanced surveillance and antihypertensive treatment, and collaborative teamwork in management. Challenges relate to the methodology of studies upon which care is based, as well as aspects of the care itself, particularly the unregulated use of home BP monitoring. Pitfalls include the unsubstantiated belief that nifedipine and magnesium sulfate cannot be used together, and the perception that severe hypertension and non-severe hypertension are separate entities rather than lying along a spectrum of BP values. The following must be addressed by future research: guidance for nuanced care as women transition between severe and non-severe hypertension, personalized antihypertensive therapy, and incorporation of women's values into research priorities and clinical practice when antihypertensive care is chosen.

***Abbreviations**:*

ACE inhibitor= angiotensin converting enzyme inhibitor
ACOG = American College of Obstetrics and Gynecology
aOR = adjusted odds ratio
ARB = (angiotensin receptor blocker
BP = blood pressure
FHR = fetal heart rate
HDP = hypertensive disorder of pregnancy
IQ = intelligence quotient
ISSHP = International Society for the Study of Hypertension in Pregnancy
LMIC = low-and-middle-income country
RCT = randomized controlled trial
SGA= small for gestational age
SMFM = Society of Maternal-Fetal Medicine

GENERAL INTRODUCTION

Hypertension complicates up to 10% of pregnancies, globally. Pregnancy hypertension is defined as systolic blood pressure (BP) ≥140mmHg or a diastolic BP ≥90mmHg, based usually on measurements in office/clinic settings and using a wide variety of BP devices and BP thresholds that correspond to two standard deviations above the mean BP throughout pregnancy. [1-3]

The hypertensive disorders of pregnancy (HDPs) are classified into three primary types: (i) chronic hypertension diagnosed before pregnancy or before 20 weeks' gestation; (ii) gestational hypertension diagnosed at ≥20 weeks; or (iii) preeclampsia, defined restrictively (and historically) as gestational hypertension with proteinuria or broadly as gestational hypertension with either proteinuria or an end-organ manifestation consistent with preeclampsia (Table 1). [4;5] There is widespread agreement on definitions other than for preeclampsia.[6]

Preeclampsia is in the differential diagnosis of any hypertension from 20 weeks' gestation. First, up to 25% of women with chronic hypertension may develop superimposed preeclampsia, and up to 35% with gestational hypertension (especially with onset at <34 weeks) may progress to preeclampsia.[7;8] Second,

preeclampsia is the HDP associated with the greatest risk of complications, involving virtually any organ system to effect adverse outcomes through endothelial cell dysfunction and the hypertension itself. Finally, preeclampsia management is more than solely antihypertensive therapy (**Table 1**),[5] mandating close interspecialty collaboration.[4]

The HDPs, especially preeclampsia, is associated with elevated maternal and perinatal risk. Antihypertensive treatment of elevated BP, in the range of 140-159/90-109mmHg and to a goal of 85mmHg diastolic, is associated with maternal benefit without increasing perinatal risk.[9] This approach applies to all HDPs and gestational age at presentation with hypertension. Of note, BP values ≥160/110mmHg, regardless of the HDP, constitute a medical urgency requiring antihypertensive therapy;[4;6] more-resourced settings are focused on determining the best initial treatment, bundling antihypertensive therapy with other aspects of management.

This review will focus on antihypertensive therapy of the HDPs as a specific strategy within broader management that includes preeclampsia prevention among women with chronic hypertension and preeclampsia management.[5]

CLINICAL NEEDS IN THIS FIELD

- ***Accurate measurement of BP***

BP measurement techniques are the same in and outside pregnancy, including positioning and correct cuff size.[10] However, the choice of the BP device used is context-sensitive.

The general withdrawal of mercury sphygmomanometers has left maternity care providers with the choice of using aneroid or automated devices. (An accurate liquid crystal sphygmomanometer has been developed, but is not yet widely available.)[11] Up to 50% of aneroid devices give inaccurate BP readings >10 mmHg through failure to maintain six-monthly calibration and resultant calibration drift; whereas

the same error occurs in only 10% of mercury devices.[12] Also, many automated devices are inaccurate in pregnancy and most are inaccurate in preeclampsia;[13] on average, underreading by 5 mmHg in systolic and diastolic, although there is wide variation.[14] A list of validated devices is available online [http://www.dableducational.org/index.html]; to date, few have been validated for use in pregnancy or preeclampsia specifically.

Out-of-office measurements, particularly self-measurements at home, should play a key role in diagnosis of hypertension in pregnancy, as in non-pregnancy; however, self-measurement is largely driven by patient interest. The widespread, largely unregulated, use of personal devices is a major challenge for maternity care (as discussed below).

- ***Agreed-upon classification of the HDPs***

There is widespread consensus that both systolic and diastolic BP should be included in the definition of hypertension in pregnancy, although a few societies use only the diastolic criterion.[6] The International Society for the Study of Hypertension in Pregnancy (ISSHP) has emphasized the need to repeat BP measurement over a few hours to confirm hypertension, or in 15 minutes if BP is severely elevated (i.e., systolic BP ≥160mmHg or diastolic BP ≥110mmHg).[4]

In pregnancy there are no designations of either 'elevated BP' (i.e., systolic BP 120-129mmHg with diastolic BP <80mmHg) or Stage 1 hypertension (i.e., BP of 130-139/80-89mmHg) as designated outside pregnancy.[10]

By non-pregnancy standards, defining severe hypertension from a systolic BP of 160mmHg is low. This threshold was established based on risk identified in an influential case series of women with stroke in pregnancy.[15] It is unclear whether pregnant women with hypertension are more susceptible to stroke because hypertension can develop very quickly or because of the endothelial dysfunction of preeclampsia, but it is clear that autoregulation and BP level are not closely related.[16]

The ISSHP classifies the HDPs into groups depending on when in pregnancy elevated BP is documented, whether it is persistent, and whether there are features suggestive of preeclampsia (**Table 2**). ISSHP guidelines differ from some national guidelines by formally recognizing white-coat, masked, and transient hypertension as distinct entities.

The internal medicine community is familiar with white-coat hypertension, and it should be managed in a similar way as outside pregnancy, relying on out-of-office measurements to guide antihypertensive therapy when women are outpatients. However, when women become inpatients (including for labor and delivery), clinicians have no choice but to treat BP measurements taken in hospital. While the medical community should also be familiar with masked hypertension, and would seek out-of-office BP measurement in the face of unexplained chronic kidney disease, for example, maternity care providers are unlikely to seek out-of-office BP measurements in the face of unexplained pregnancy complications that could be attributable to the HDPs (e.g., fetal growth restriction).

ISSHP has emphasized the importance of transient hypertension, because it is not just elevated BP that was demonstrable because of poor measurement technique. Rather, transient gestational hypertension is associated with a 40% risk of developing true gestational hypertension or preeclampsia at some point in that pregnancy, mandating close follow-up.[4]

- ***Agreed-upon thresholds for action***

For the mother, any hypertension is associated with more adverse outcomes, in virtually any organ system [17], from pulmonary edema and acute kidney injury, to central nervous system complications, including stroke [18;19]. Both systolic and diastolic BP are important predictors of stroke, although variably associated.[15;20] Also, the HDPs remain a leading causes of maternal death globally.

For the fetus/newborn, the HDPs are associated with stillbirth, neonatal death, and neonatal morbidity of various severity (depending on gestational age at birth and fetal growth).

While studies have evaluated BP as a continuous measure, recent data from the CHIPS trial of women with chronic or gestational hypertension show that development of severe hypertension among women with prior non-severe hypertension is associated with elevated risk for both mother and baby, independently of any concomitant preeclampsia.[9]

- ***Close collaboration with maternity care colleagues***

Standardized care and teamwork are particularly relevant during maternity care, a brief scenario by other medical standards (i.e., maximum duration of nine months of pregnancy and six weeks postpartum), and often delivered by many individuals with different skill sets. Standardization of complex care has been particularly topical within maternity services in the United States, given the upturn in maternal mortality, one of the leading causes of which is the HDPs (alongside postpartum hemorrhage and obstetric sepsis). 'Bundles' of complex care include management of severe hypertension [21]. The bundle goes beyond the 'response' of antihypertensive therapy and both escalation measures for those unresponsive to standard treatment and postpartum follow-up, to reporting and systems learning, readiness, and recognition and prevention.

SCIENTIFIC OVERVIEW OF PRECLINICAL AND CLINICAL STUDIES

Antihypertensive treatment of hypertension in pregnancy is guided by many randomized controlled trials (RCTs), although most have been small and many of low quality.[22;23] These trials have enrolled women with a variety of hypertensive disorders, although when women were enrolled at ≥20 weeks' gestation, trials often did, or could, not distinguish between women with chronic hypertension and women with gestational hypertension or preeclampsia that, by definition, arose ≥20 weeks. Thus, the global guideline consensus is that clinicians respond to absolute BP levels, regardless of the underlying HDP.

The implications of hypertension for the mother and baby depend both on the absolute level of BPand the rate with which it has risen. An abrupt increase in intraluminal pressure may result in mechanical distension of the cerebral vessel wall and structural damage, as, in cats, an abrupt (vs. step-wise) increase in BP is associated with greater cerebrovascular permeability - a measure of vascular injury.[24]

- ***Antihypertensive treatment of severe hypertension (BP ≥160/110mmHg)***

Consistently, national and international guidance recommends that severe hypertension in pregnancy requires antihypertensive therapy to avoid acute cerebrovascular complications, particularly stroke [6;25].

As in the non-pregnant state, severe hypertension unassociated with end-organ complication is usually a medical 'urgency'; and BP can be lowered over hours. In contrast, women with an end-organ complication(s), such as pulmonary edema or acute kidney injury, should have their BP lowered over a shorter time frame; to be conservative, women with headache and visual symptoms should be regarded as having end-organ complications.[18]

As for non-pregnancy, the goal should be lowering to non-severe levels (i.e., <160/110mmHg) over hours without reducing it by more than 25% initially, with subsequent gradual lowering over hours thereafter. The fetoplacental unit, which does not autoregulate blood flow, is at risk of underperfusion during this time; appropriate fetal heart rate (FHR) monitoring should be instituted by the obstetrician or his/her designate. The intravascular volume depletion of preeclampsia can precipitate hypotension following short-acting antihypertensive agent administration.

Antihypertensive treatment of severe hypertension in pregnancy is guided by 52 RCTs (4588 women) of one short-acting antihypertensive vs. another, usually parenterally administered (other than of oral nifedipine.)[26-33] Most published trials have compared parenteral hydralazine (usually 5mg iv) with either calcium channel blockers (usually nifedipine 10mg capsules orally) or parenteral labetalol (usually 20mg iv) with repeat doses administered every 15-20 minutes in order to achieve BP control in at least 80% of

women; in 10 trials, hydralazine was compared with drugs available only regionally or used infrequently. These dosing regimens are more conservative than those recommended by the American College of Obstetrics and Gynecology (ACOG) which advises that clinicians administer the drugs in escalating doses to achieve the target BP goals.[34]

Hydralazine may be a less effective antihypertensive and associated with more maternal side effects, compared with calcium channel blockers. Hydralazine may be a more effective antihypertensive but associated with more maternal hypotension and side effects, compared with parenteral labetalol. Most of the published hydralazine trials were included in a 2003 meta-analysis that compared hydralazine with all other short-acting antihypertensive agents taken together; hydralazine was associated with more adverse effects, including maternal hypotension, Cesarean delivery, and adverse FHR effects.[27] It should be noted that in two hydralazine vs. labetalol trials, parenteral labetalol was associated with more neonatal bradycardia (which required intervention in one of six affected babies in one trial).

Oral nifedipine and parenteral nicardipine appear to be similarly effective for BP control compared with parenteral labetalol.[32;33] The nifedipine preparations that are appropriate for treatment of severe hypertension are the capsule and the intermediate-acting (PA) tablet,[35] where available. Most authors did not specify whether nifedipine capsules were bitten (prior to swallowing), which may have a greater effect on BP. The 10mg tablet may be associated with less maternal hypotension than the 10mg capsule when it is bitten/punctured [35;36]. The 5 mg capsule may reduce the risk of a precipitous fall in BP.[37;38] The effectiveness of nifedipine may be enhanced by concomitant vitamin D[39] or, postnatally, by concomitant furosemide.[40]

As most women with severe hypertension in pregnancy have a hypertensive 'urgency' that could be treated with oral agents, those (in addition to nifedipine discussed above) that lower BP over hours could be used. Although there are limited trial data evaluating this approach,[31;41] oral labetalol (200mg)

has been used with good effect as part of a regional preeclampsia protocol in which treatment was successful in about half of women[42] or in comparison with oral nifedipine;[31] this approach is recommended as the first-line agent in the UK.[43] The results of an oral nifedipine (tablet), labetalol, and methyldopa trial will report in 2018 (NCT01912677). While evidence is lacking, oral labetalol may also be useful to administer prior to sending a woman into hospital or arranging for her transport there for further management.[44]

Drugs used both infrequently, often for refractory hypertension during critical care, include clonidine and captopril,[29] nitroglycerin infusion, mini-dose diazoxide, and sodium nitroprusside.[14] The latter may cause fetal cyanide toxicity and stillbirth.[45]

In summary, oral nifedipine, parenteral hydralazine, and parenteral labetalol are the most commonly studied antihypertensive agents for severe hypertension. As none is clearly superior, each is a reasonable choice, in doses listed in **Table 1**. Some antihypertensives may be more or less appropriate based on associated medical conditions (such as poorly-controlled asthma) or therapies (such as current treatment with full doses of labetalol).

The antihypertensives discussed here can be used with other medications. Nifedipine can be used together with magnesium sulfate as neuromuscular blockade in this setting is rare.[46] Magnesium sulfate is not an effective antihypertensive agent, although it can cause a transient, mild decrease in BP.[47]

Antihypertensive therapy for non-severe hypertension (BP 140-159/90-109mmHg)

Choice of antihypertensive agent in early pregnancy

Women with chronic hypertension will be treated with antihypertensive therapy before or in early pregnancy. Teratogenicity (i.e., increased risk of major birth defects) and miscarriage risk should be considered and a decision made as to whether therapy should be discontinued or switched to another agent before pregnancy. Approximately half of pregnancies are unplanned; prescribers must consider

the potential for pregnancy in all hypertensive women of reproductive age. If medication is to be discontinued or replaced prepregnancy, a further consideration is that conception may normally take up to 12 months, and women over 30 years of age suffer more subfertility. Therefore, women could be off their medication for some time; when renoprotection is the goal, timelines are suboptimal. In addition, women who have had an inadvertent first trimester exposure to antihypertensive therapy should be counseled about their risks.

Based on limited literature, most antihypertensives do not increase the risk of major malformations above the baseline risk of 1-5%, or the miscarriage rate of up to 20%. This concept of baseline risk is critical to communicate, as many women assume that their risk of early pregnancy problems is zero if they do not take medication.

No antihypertensive medication is a proven human teratogen. Initial associations between angiotensin converting enzyme (ACE) inhibitors and birth defects may have suffered from residual confounding.[48] Subsequent work has been variably reassuring. ACE inhibitors or angiotensin receptor blockers (ARBs) have been associated with miscarriage (but not birth defects) in a prospective cohort study of 138 women, compared with both hypertension and normal pregnancy controls; most of the women (79.8%) were exposed to ACE inhibitors (usually ramipril, lisinopril, or enalapril) rather than ARBs.[49] ACE inhibitors, ARBs, *and* other antihypertensive agents have been associated with teratogenicity in a meta-analysis of five controlled cohort studies (786 infants exposed to ACE inhibitors or ARBs, 1723 exposed to other antihypertensives, and 1,091,472 unexposed).[50] UK clinical practice guidelines state that thiazides are teratogenic, but a reference was neither provided nor identified.[43]

In summary, given the lack of consistent and high-quality literature, it is considered acceptable to continue antihypertensive agents, including ACE inhibitors and ARBs, until conception.

Threshold for treatment in ongoing pregnancy

There have long been concerns that antihypertensive treatment of non-severe hypertension would decrease uteroplacental perfusion and fetal nutrition, leading to adverse fetal and newborn outcomes; an argument strengthened by a metaregression analysis that associated greater antihypertensive-induced falls in mean arterial pressure with decreased fetal growth velocity.[51;52] The CHIPS trial (Control of Hypertension In Pregnancy Study) tested this hypothesis.[9]

CHIPS was a large definitive trial that provided evidence that non-severe hypertension in pregnancy should be treated with antihypertensive therapy [9]. CHIPS enrolled women with chronic (75%) or gestational (25%) hypertension, but superimposed preeclampsia developed in almost half of women, and they continued to receive the BP treatment to which they were randomized for two subsequent weeks prior to delivery; therefore, it is reasonable to apply the results to all hypertensive pregnant women. Women with co-morbidities such as renal disease and pre-gestational diabetes were excluded; 'tight' control is advocated for them to reduce progression of renal disease and long-term cardiovascular risk, as outside pregnancy.[10] 'Tight' BP control (target diastolic BP 85mmHg) (vs. 'less tight' control, target diastolic BP 100mmHg) achieved a significantly lower BP by 6/5mmHg, through use of a simple treatment algorithm for 'tight' control that resulted in a mean BP of 133/85mmHg; antihypertensive therapy was decreased if diastolic BP fell below 80mmHg, as is frequently encountered with the mid-pregnancy fall in BP.[9] 'Tight' (vs. 'less tight') control resulted in similar rates of the adverse perinatal outcomes and birth weight <10th percentile. However, 'tight' (vs. 'less tight') control resulted in fewer adverse maternal outcomes of severe maternal hypertension, platelet count <100x10^9/L, and symptomatic elevated liver enzymes; there was no difference in serious maternal (end-organ) complications. Post-hoc analyses determined that severe hypertension, independent of any associated preeclampsia, was a risk factor for complications for the mother and the baby, and in the 'less tight' control arm specifically, severe hypertension was associated with more serious maternal complications

[53]. Women in 'tight' (vs. 'less tight') control were equally satisfied with their care.[54] 'Tight' control was likely to be cheaper by an average of CAD$6000, based on lower neonatal care costs (p=0.07).[55]

The results of the CHIPS trial are consistent with existing small trials that have shown that antihypertensive therapy (similar to 'tight' control in CHIPS), compared with no treatment or placebo (similar to 'less tight' control in CHIPS), decreases the risk of severe hypertension.[22] Women enroled were usually without co-morbidities, and a wide variety of antihypertensive agents (started after the first trimester of pregnancy) were evaluated: methyldopa, labetalol, other pure beta-blockers (acebutolol, mepindolol, metoprolol, pindolol, and propranolol), calcium channel blockers (isradipine, nicardipine, nifedipine, and verapamil), hydralazine, prazosin, and ketanserin.[22] This bodes well for women who have a contraindication to a particular medication, such as labetalol because of poorly-controlled asthma.

The 2018 ISSHP recommendations[4] endorse commencement of antihypertensives for persistent non-severe hypertension well before BP reaches 160/110mmHg mark, an approach that seeks to reduce the likelihood of developing severe maternal hypertension. An editorial pointed out that, "to manage BP expectantly at <160/110 mmHg but emergently at $\geq$160/110 mm Hg is logically inconsistent"; ISSHP supports this perspective.[56] However, the American Society of Maternal-Fetal Medicine (SMFM) is awaiting the results of the CHAP Trial in 2020/21(NCT02299414) before advising on treatment of non-severe chronic hypertension. CHAP is enrolling women with chronic hypertension and randomizing them to treatment approaches similar to CHIPS. CHAP will be powered to address whether 'tight' control has additional benefits for the mother (i.e., fewer serious maternal complications) or more side effects for the baby (i.e., SGA infants), but not whether there is a difference in pregnancy loss or morbidity.[57]

With few exceptions, trials have initiated therapy with one antihypertensive agent. Clinicians are concerned about dropping BP too low, overriding knowledge that outside pregnancy, monotherapy will

be insufficient to control BP if it is more than 20/10mmHg above the target BP.[10] In pregnancy, successful treatment of hypertension occurs in more than 70% of women who are primarily treated with one agent;[22] the corresponding success rate is 30-50% outside pregnancy.

Choice of antihypertensive agent for BP control

ACE inhibitors and ARBs should be discontinued once pregnancy is confirmed, because of toxic effects, especially renal. If used prior to pregnancy for renoprotection, there is no reasonable alternative available in pregnancy; it is noteworthy that most renoprotection is afforded by 'tight' control of BP using any agent.

There is little to guide the choice of antihypertensive agent in pregnancy based on comparative trials of one antihypertensive agent vs. another. Meta-analysis, and subsequent small trials, have revealed no clear differences in maternal and perinatal outcomes.[22;58-60] Compared with methyldopa, alternative drugs studied (i.e., beta-blockers and calcium channel blockers) may be more effective at reducing the risk of severe hypertension or preeclampsia. However, results for preeclampsia are inconsistent, and no firm conclusions can be drawn. Beta-blockers, but not calcium channel blockers, may decrease the risk of preeclampsia compared with placebo/no therapy; however, when beta-blockers and calcium channel blockers were compared directly, beta-blockers did not decrease preeclampsia as would have been expected. Of note, in the CHIPS Trial, women treated with methyldopa (vs. labetalol) may have had *better* maternal and perinatal outcomes, although there may have been residual confounding.[61]

Methyldopa, labetalol, and nifedipine, in doses listed in **Table 2**, are the most commonly recommended antihypertensive agents in international practice guidelines, although oral labetalol is not widely available in low-and-middle-income countries (LMICs).[62] Vitamin D has been reported to enhance the effectiveness of nifedipine.[39] Thiazide diuretics can be considered for hypertensive women, but their use is limited to specific circumstances, such as medullary sponge kidney, despite concerns that they may

inhibit the normal plasma volume expansion of pregnancy. Thiazide use after the first trimester did not adversely affect maternal or perinatal outcomes, or prevent preeclampsia.[63]

Some antihypertensives may be best avoided in pregnancy, although not without controversy. Atenolol (in contrast to other, even cardioselective, beta-blockers) may reduce fetal growth velocity;[64-67] an inconsistent observation.[68] Prazosin was associated with more stillbirths in early severe preeclampsia.[69] Oral hydralazine is not recommended because of side effects when used alone.[70]

There is an unsubstantiated belief that oral methyldopa may decrease fetal alertness and movement, or FHR variability, and oral labetalol may decrease FHR and variability;[71] prudently, changes in FHR or pattern should be ascribed to evolution of underlying disease, and not prescribed antihypertensive(s).

Postpartum antihypertensive therapy

Blood pressure consistently rises from days 3-6 postpartum. Postpartum, hydralazine, labetalol, and nifedipine have been used for severe hypertension;[72] all are appropriate during breastfeeding. Nifedipine may be more effective postnatally when administered with furosemide.[40] Some ACE inhibitors, acceptable during breastfeeding, can be restarted after delivery (such as enalapril and quinapril). Captopril is effective outside pregnancy but studied postpartum only in critical care.[29;31;73] Neonatologists have reservations in babies born early or small, but there are no reports of adverse effects. Only two antihypertensives are not recommended for use during breastfeeding: sodium nitroprusside because toxic metabolites (thiocyanate and cyanide) may cross into breast milk, and oral clonidine because of high serum drug levels in breastfed infants.[73] Information on drugs and breastfeeding is freely available in the LactMed database.[73]

Long-term paediatric neurodevelopmental outcomes

The potential long-term developmental effects of antihypertensive therapy in pregnancy have been understudied. Most studies do not address important confounders of the relationship between

outcomes and antihypertensive therapy, key among which is the type of HDP. Children of women with gestational hypertension or preeclampsia appear to have a relatively modest, inconsistent increase in neurodevelopmental problems, such as inattention and externalizing behaviors (e.g., aggression), fine or gross motor function, or verbal ability;[74-77] outcomes after chronic hypertension are unknown. Limited data from a few small RCTs are reassuring with regards to health or neurodevelopment at: 12-18 months of age following nifedipine[78] or atenolol,[79] or 7.5 years following methyldopa.[80] Data from a controlled observational study presented reassuring data for labetalol (N=32 pregnancies). Compared with women exposed to medications without known neurodevelopmental effects (N=42), children with in utero methyldopa exposure (N=25) had slightly lower intelligence quotient (IQ) scores within the normal range, related methyldopa treatment duration.[81]

CHALLENGES AND PITFALLS RELEVANT TO THE TOPIC

Composite and surrogate outcomes

Of primary interest to clinicians and women is the impact of antihypertensive therapy on maternal, fetal, and newborn death and serious complications. For the mother, these include death, obstetric complications such as abruption, and end-organ complications (such as stroke).[17;82] For the fetus and newborn, relevant outcomes are stillbirth, neonatal death and life-threatening morbidity. Thankfully, these complications are individually uncommon or rare, but this situation poses a problem for researchers. Studying the impact of antihypertensive therapy on an individual complication (such as stroke) is not feasible, and even if it were, such a focus may reflect an arbitrary choice of outcome that does not reflect the spectrum of considerations at play. Also, the balance of benefit and risk may change with gestational age, as do outcomes of relevance; for example bronchopulmonary dysplasia is only possible if birth occurs before 32 weeks, and hypoxic-ischemic encephalopathy possible if birth occurs at

term. Gestational age is also important for the mother, as the implications of severe hypertension as an outcome are different at 25 weeks in the setting or early severe preeclampsia, compared with term, as the gains from pregnancy prolongation vary.

As a response to these challenges, researchers have often studied surrogate outcomes (such as preeclampsia or preterm birth), or composites of rare complications. This challenge to evidence syntheses often results in few trials in subgroups of outcomes, and uncertainty about whether the effects observed are influenced by reporting biases.

It is hoped that these challenges in outcome measurement will be addressed by the international movement towards standardization. Development of a core outcome dataset in preeclampsia is nearing completion.[17]

The unregulated use of HBPM

Recently, HBPM has gained popularity outside pregnancy in confirming hypertension, and improving BP monitoring, compliance with antihypertensive medication, and achievement of BP targets.[83] Compared with ambulatory BP monitoring, HBPM has modest diagnostic agreement, is similar in its ability to identify patients with 'white coat' effect and 'masked' hypertension, and is economical and comfortable. Distinct advantages of HBPM in pregnancy are patient engagement, and the ease with which repeat measurements can be obtained, especially to rule out preeclampsia superimposed on either chronic or gestational hypertension.[84] Pregnant women and practitioners prefer HBPM to ABPM.[85]

While HBPM is widely used, by more than half of hypertensive women in some studies,[9] it is not widely appreciated by women or maternity care providers that what defines normal BP in the office (i.e., ≥140/90mmHg) is higher than what defines normal BP at home (i.e., ≥135/85mmHg), even in pregnancy [4;86]. Also, practitioners do not usually advise women about available monitoring schedules, all of which involve duplicate measurements taken at least twice daily over several monitoring days.[10;87] Many

women take it upon themselves to measure their own BP. In addition, women are not necessarily educated about interpretation of the values recorded, including when and whom to call about BP values above a given threshold.[14]

Nifedipine and magnesium sulfate co-administration

Among women with preeclampsia among whom magnesium sulfate is indicated for eclampsia prevention or treatment, the risk of neuromuscular blockade (reversible with 10 g of IV calcium gluconate) with contemporaneous use of nifedipine and magnesium sulfate is <1%.[46]

UNRESOLVED CLINICAL QUESTIONS

Nuanced antihypertensive therapy for severe and non-severe hypertension

Although antihypertensive therapy for severe hypertension has (with few exceptions) been with parenteral agents other than oral (usually short-acting) nifedipine, and therapy for non-severe hypertension has been with oral agents, women with a HDP transition from one severity of hypertension to another. Severe and non-severe hypertension are not separate clinical entities, as are chronic hypertension and preeclampsia, for example. Clinical guidance has yet to address nuanced care reflecting clinical complexity or the large number of care providers. Direction about dosage escalation and choice of multidrug antihypertensive treatment is lacking. While, NICE guidance (UK) advises that oral labetalol be used as first-line therapy for hypertension of any severity, it may not be sensible to give a woman additional oral labetalol when she is already on 1600mg/day and presents with severe hypertension.

Personalized antihypertensive therapy

Outside pregnancy different mechanisms underlie essential hypertension: either high renin and vasoconstriction or low renin, volume-expansion.[88] Patients of black race tend to fit into the low renin category. While this knowledge influences choice of antihypertensive outside pregnancy, there is no similar guidance in pregnancy. Indeed, oral labetalol is considered an acceptable first-line agent for all pregnant women, even in settings where the prevalence of women of black race is high (e.g., the UK).

What about maternal hemodynamics assessment in hypertensive pregnant women? When assessed from the time of referral for hypertension (usually after 20 weeks' gestation) women whose BP was controlled (to <140/90mmHg) with labetalol monotherapy had higher heart rate and stroke volume (and were less like to be of black race),[89] compared with women requiring additional vasodilatory treatment with nifedipine.[90] Those requiring the vasodilatation also experienced more severe hypertension and smaller babies. In 52 drug-naïve pregnant women with various hypertensive disorders (38.5% chronic), when initial antihypertensive therapy was guided prospectively by hemodynamics, using initial nifedipine therapy when vascular resistance was high or women were of black race,[91] and labetalol otherwise to achieve BP <140/90mmHg, the incidence of severe hypertension was low (3.8%) without compromising fetal growth.[92] Such a personalized approach based on hemodynamic assessment holds promise to optimize fetal growth for women receiving 'tight' control of BP. However, more information is needed about feasibility, cost implications, and effectiveness.

The patient voice

Antihypertensive treatment has a clinically meaningful impact on maternal risk profiles, without adversely affecting the baby's risk profile or the woman's satisfaction with her care. However, the strength of recommendations is often weak and the quality of the evidence low. Therefore, optimal decisions about BP control will depend on how each woman trades-off (i.e., values) her own vs her child's outcomes, and how those values would change depending on the gestational age at which they

would need to be made. Currently, we lack the data to develop patient decision aids to help clinicians structure information and work with women to encourage them to evaluate all decision options and their consequences in accordance with their values without bias, and to make a decision based on those trade-offs. Also, we lack the data to measure value-weighted outcomes (which would be of particular relevance to composite outcomes). Lastly, we need our research to priority-setting that involves input from all stakeholders, including women and their families, so that BP management research asks questions of relevance to women and measures outcomes that will inform their decision-making.

CONCLUSIONS

Internationally, antenatal care is devoted in large part to the detection of pre-eclampsia by measurement of BP. The withdrawal of mercury sphygmomanometers has created a major challenge for accurate measurement of that BP, as aneroid devices are less accurate and most automated devices underestimate BP in pregnancy and pre-eclampsia, specifically. When elevated BP is detected, regardless of the HDP, antihypertensive therapy to achieve a diastolic BP of 85mmHg will decrease maternal risk without increasing perinatal risk. This antihypertensive therapy will of course be embedded in broader, multifaceted management of the mother and fetus.

Future work should focus on whether one antihypertensive drug offers advantages over another in general or for specific ethnic groups in pregnancy, and whether hemodynamic-guided antihypertensive therapy can optimise fetal growth and actually *improve* perinatal outcome.

Table 1: The ISSHP classification of the HDPs

Hypertension known before pregnancy or before 20 weeks' gestation	**Definition**
Chronic	Elevated BP before pregnancy or before 20 weeks' gestation
Essential	Without a recognized underlying cause
Secondary	Due to underlying problem, such as renal disease
White coat hypertension	Elevated BP in office/clinic, but normal BP in out-of-office setting (including at home)
Masked hypertension	Elevated BP in out-of-office setting, but normal BP in office/clinic
Hypertension arising de novo at or after 20 weeks	**Definition**
Transient gestational hypertension	Elevated BP documented, usually in office/clinic, but follow-up BP measurements are normal, often in day assessment units or at home
Gestational hypertension	Elevated BP at ≥20 weeks' gestation
Pre-eclampsia	Gestational hypertension with proteinuria or one/more manifestations suggestive of end-organ involvement[a]
De novo	
Superimposed on chronic hypertension	

HDPs=hypertensive disorders of pregnancy, ISSHP=International Society for the Study of Hypertension in Pregnancy

[a]End-organ involvement with pre-eclampsia includes, but is not limited to, neurological, respiratory, hepatic, and renal.

Table 2: Management of pre-eclampsia (Adapted from the *Lancet*[5] with permission)

Antepartum and postpartum (unless otherwise specified)	
Place of care	**Inpatient** care when there is severe hypertension or maternal symptoms, signs, or abnormal laboratory tests
	Outpatient care can be considered, recognisizg that many women are not eligible and hospital re-admission rates are high following home care
Consultation	**Obstetrics** to ensure that preeclampsia risk is recognized and appropriate maternal and fetal surveillance is put in place
	Anesthesia to plan maternal monitoring and plan neuraxial analgesia/anesthesia in labour to assist with BP control and facilitate Cesarean delivery (should it be necessary)
Fluid management	**Restrict** to a maximum of 80mL/hr when an iv is in place.
Antihypertensive therapy	**Severe hypertension (BP ≥160/110mmHg):** Consider oral or parenteral agents that can be repeated in 30min if BP remains at ≥160 mmHg systolic or ≥110 mmHg diastolic: • Nifedpine capsule (10mg orally without biting to a maximum of 30mg) • Nifedipine tablet (10mg orally to a maximum of 30mg) • Hydralazine (5mg iv bolus then if needed, 5-10mg iv to a maximum of 45mg) • Labetalol (20mg iv then if needed, 40mg then 80mg to a maximum of 300mg) Consider alternative oral agents that can be repeated in 1 hr (supported by less evidence in pregnancy): • Labetalol (200mg orally) • Clonidine (0.1 - 0.2mg orally)[a] • *Only postpartum* - Captopril (6.25 - 12.5mg orally)
	Non-severe hypertension • Methyldopa (500-2000mg/d in 3 or 4 divided doses) • Labetalol (300-2400mg/d in 3 or 4 divided doses) • Nifedipine (20-120mg/d once daily)
$MgSO_4$	**Eclampsia *treatment*** • 4g iv (over 5 min) then 1g/hr iv • If already on $MgSO_4$, administer another 2-4g iv (over 5 min) and increase infusion to 2g/hr iv
	Eclampsia *prevention* among women with pre-eclampsia • 4g iv (over 5 min) then 1g/hr iv
	Fetal neuroprotection

	4g iv (with/without 1g/hr until delivery or 24hr maximum) for women with imminent delivery at $<34^0$ weeks who do not otherwise quality for eclampsia prevention or treatment
Corticosteroids	Antenatally only, for **fetal pulmonary maturity** when delivery is anticipated within the next 7 days and at $<34^{0-6}$ wks
	HELLP syndrome (10mg dexamethasone IV every 12h for 48h) if improvement in laboratory parameters alone will change management, such as eligibility for neuroaxial anesthesia/analgesia or platelet transfusion
Platelet transfusion for HELLP syndrome	Recommended for counts: $<20x10^9$/L, 20-$49x10^9$/L prior to Cesarean, or $\geq 50x10^9$/L (± packed red blood cells) with excessive active bleeding, platelet dysfunction, a rapidly falling platelet count, or coagulopathy.

HELLP=Hemolysis, Elevated Liver enzyme, Low Platelet syndrome; iv=intravenous; $MgSO_4$=magnesium sulphate

[a]Clonidine therapy is not recommended during breastfeeding (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm).

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